09/890488

corrected

10

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

**(PCT Article 36 and Rule 70)**



| Applicant's or agent's file reference | **FOR FURTHER ACTION** | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| 16230-9004 | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/US00/03488 | 08 FEBRUARY 2000 | 08 FEBRUARY 1999 |

International Patent Classification (IPC) or national classification and IPC
IPC(7): A61F 2/04, 2/06; C08G 63/91; C08J 9/26 and US Cl.: 600/36; 623/1; 521/61; 528/370

Applicant
BIOAMIDE, INC.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

CORRECTED VERSION

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 07 SEPTEMBER 2000 | 12 FEBRUARY 2001 |
| Name and mailing address of the IPEA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231 | Authorized officer<br>Carol Krdull fi<br>ISIS GHALI |
| Facsimile No. (703) 305-3230 | Telephone No. (703) 308-1235 |

Form PCT/IPEA/409 (cover sheet) (July 1998)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/03488

## I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed

☒ the description:
pages (See Attached), as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:
pages (See Attached), as originally filed
pages _____, as amended (together with any statement) under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the drawings:
pages (See Attached), as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the sequence listing part of the description:
pages (See Attached), as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/03488

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. statement**

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 6-10, 12-15, 18-25, 27-36 | YES |
| | Claims | 1-5, 11, 16, 17, 26 | NO |
| Inventive Step (IS) | Claims | none | YES |
| | Claims | 1-36 | NO |
| Industrial Applicability (IA) | Claims | 1-36 | YES |
| | Claims | none | NO |

**2. citations and explanations (Rule 70.7)**

Claims 1-5, 11, 16, 17 and 26 lack novelty under PCT Article 33(2) as being anticipated by Tang et al. (US 5,486,593) the reference disclosed bioabsorbable fibers or devices comprising a porous sheath of glycolic acid and a solid core of glass or titanium for introducing an agent into a living host and a method for their production.

Claims 1-36 lack an inventive step under PCT Article 33(3) as being obvious over Tang et al. (US 5,486,593). The reference teachings discussed above. However, the reference does not teach the living cells from hair follicles as the active agents in the device. Thus, it would have been obvious to one having ordinary skill in the art at the time the invention was made to include living cells in the filaments or devices as an active agent motivated by the general knowledge in the art and according to the specific need of the device with reasonable expectation of success of the delivered device to be used as different kinds of implants.

Claims 1-36 meet the criteria set out in PCT Article 33(4) for industrial applicability. A device for treating male pattern baldness well have a use in cosmetic medical field.

Applicant traversing the written opinion on lack of novelty of claims 1-5, 11, 16, 17 and 26 and lack of inventive steps of claims 1-36 over Tang et al. by arguing that the reference did not disclose solid core and porous sheath nor the poly(glycolic acid).

In response to the above argument, the examiner is pointing out to col.7, lines 6-37; col.8, lines 36-52; col.18, line 24 till col. 19, line 9, where the reference disclosed fibers composed of sheath-core compartment, col.7, lines 10-11. Also, the reference in col.8, lines 37-42 disclosed coating of fibers, which is forming a sheath. Furthermore, the reference in col.18, line 63, is teaching poly(glycolide).

---------- NEW CITATIONS ----------

NONE

**Supplemental Box**
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII



I. BASIS OF REPORT:

This report has been drawn on the basis of the description,
page(s) 1, 2, 4-7, and 9-20, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
Pages 3 and 8, filed with the letter of 04 January 2001.

This report has been drawn on the basis of the claims,
page(s) 22, 23, and 25, as originally filed.
page(s) NONE, as amended under Article 19.
page(s) NONE, filed with the demand.
and additional amendments:
Pages 21, 24 and 26, filed with the letter of 04 January 2001.

This report has been drawn on the basis of the drawings,
page(s) 1-9, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the sequence listing part of the description:
page(s) NONE, as originally filed.
pages(s) NONE, filed with the demand.
and additional amendments:
NONE

surgery or other painful and expensive implantation techniques, preferably, a technique which produces hair which looks realistic and similar to other hair on the same host. The present invention utilizes a modified form of the bioabsorbable polymeric means developed for use in implantable devices, as described above, to deliver hair follicle cells transdermally and to promote the regeneration of hair therein.

As is shown in the next section, below, the present invention provides a new means for the introduction of agents into a living host, a means which offers several advantages over known means in use today, such as those described briefly above.

## BRIEF SUMMARY OF THE INVENTION

The present invention provides a filamentary means for the introduction of agents into a living host, comprising a filament comprising a solid core and a porous sheath which coats at least a portion of the solid core. When the filamentary means is to be permanently implanted into a living host, both the solid core and the porous sheath are bioabsorbable. When the filamentary means is to be temporarily implanted into the skin of a living host to deliver agents, such as cells, therein, the porous sheath is preferably bioabsorbable but the core need only be biocompatible, not bioabsorabable.

The solid core is preferably wire when the filamentary means is designed to be used to deliver an agent, such as hair follicle cells, into the skin of a living host. The solid core is preferably glass or ceramic when the filamentary means is to be used to deliver an agent, such as cells or pharmaceutical agents, into bone through implantation of the filamentary means into the body of the host.

The porous sheath is preferably in the form of reticulated foam that is well adhered to the core but is capable of separating from the core after a period of several days in vivo. When the agent to be delivered with the filamentary means is a drug, the porous sheath is preferably in the form of a hydrogel and the porosity is on a molecular size scale.

The filamentary means of the present invention provides means for delivery of cells or other agents from outside the body of a living host into the skin of the host, such as a mammal, with minimal trauma to the host. When the filamentary means is comprised of a bioabsorbable core with a bioabsorbable porous sheath which coats at least a portion of the core, the filamentary means can be implanted into specific tissue within a living host and used to deliver agents to the specific tissue when implanted therein. The implantable embodiment of the filamentary means can serve as a surface for osteoblast

skin only long enough for the porous coating to soften and detach from the solid core, but not long enough for the epidermis (8) to grown down the outside of the filament.

FIG. 5b depicts the implant site after the filament core has been removed by pulling out the semi-rigid backing to which it was attached as shown in FIG. 5a. In this case, pulling out the semi-rigid backing and core has resulted in separation of the cell laden porous sheath (2) from the solid core. Sufficient time has elapsed that the epidermis (8) has grown over the implant site, the porous bioabsorbable coating has resorbed, and the implanted cultured cells (6) have survived and are functioning properly.

FIG. 6 is a schematic representation of filaments comprised of a solid core (1) and a porous coating (2) that are bonded together. The process that is utilized to create the bonds between the filaments, for example by heating and cooling, preferably is the same process that is used to create porosity in the coating

FIG. 7 is a scanning electron micrograph (SEM) of the device described in Example 1, at a scale of 1 mm.

FIG. 8 is an SEM of the device described in Example 1, viewing the wires on end showing the exposed tips of the wires and the surrounding coatings of porous, bioabsorbable polymer, at a scale of 100 μm.

FIG. 9 is an SEM of the end of a single wire of the device described in Example 1, showing the morphology of the porous coating, at a scale of 20 μm.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention provides filamentary means for delivery of various agents into a living host, a means comprising a filament comprising a solid core and a bioabsorbable porous sheath. When the solid core is made of bioabsorbable material, it is preferably material selected from the group consisting of glass, ceramic, and polymeric material. When the solid core is made of a biocompatible material, it is preferably material selected from the group consisting of metals or alloys containing the elements of iron, nickel, aluminum, chromium, cobalt, titanium, vanadium, molybdenum, gold, and platinum. The core of the filamentary means is preferably made of bioabsorbable material when the filamentary means is to be used as or as part of an implant to be permanently implanted into the body of a living host. The core of the filamentary means is preferably made of biocompatible material when the filamentary means is to be used in the

CLAIMS

1. A filamentary means for the introduction of an agent into a living host, comprising a filament comprising a solid core and a porous sheath, wherein the porous sheath comprises a bioabsorbable sheath polymer which coats at least a portion of the solid core.

2. The filamentary means of claim 1, wherein the solid core comprises a bioabsorbable material selected from the group consisting of a glass, a ceramic, and a polymer.

3. The filamentary means of claim 1, wherein when the solid core is made of a biocompatible material selected from the group consisting of metals or alloys containing the elements of iron, nickel, aluminum, chromium, cobalt, titanium, vanadium, molybdenum, gold, and platinum.

4. The filamentary means of claim 1, wherein the bioabsorbable sheath polymer is selected from the group consisting of poly(lactic acid), poly(glycolic acid), poly(trimethylene carbonate), poly(amino acid)s, tyrosine-derived poly(carbonate)s, poly(carbonate)s, poly(caprolactone), poly(para-dioxanone), poly(ester)s, poly(ester-amide)s, poly(anhydride)s, poly(ortho ester)s, collagen, gelatin, serum albumin, proteins, carbohydrates, poly(ethylene glycol)s, poly(propylene glycol)s, poly(acrylate ester)s, poly(methacrylate ester)s, poly(vinyl alcohol), and copolymers, blends and mixtures of said polymers.

5. The filamentary means of claim 1, further comprising an agent.

6. The filamentary means of claim 5, wherein the agent is living cells.

7. The filamentary means of claim 6, wherein the living cells are obtained from hair follicles.

8. The filamentary means of claim 6, wherein the living cells are genetically engineered cells.

25. The method of claim 22, wherein the semi-rigid backing of embedded filaments is formed in step (b) according to the additional steps comprising:

inserting the first end of each filament into a mold containing holes that are spaced the same distance apart as hairs on the normal scalp and of a depth sufficient for the first end of each filament to penetrate the skin of a living host when embedded in the semi-rigid backing formed in the remaining steps below,

coating the second end of each filament protruding from the mold with a resin,

curing the resin into a solid polymer,

covering the surface of the polymer with a puncture resistant adhesive tape, and

removing the resulting device, a semi-rigid backing with an array of the first end of filaments protruding therefrom, from the mold.

26. A device for implanting cells into the skin of a living host, comprising:

a) a plurality of filaments, wherein each filament has a first end and a second end, each filament comprising a biocompatible core and a bioabsorbable porous sheath which coats the core at least at the first end of each filament, and

b) a semi-rigid backing with the second end of each of the plurality of filaments embedded therein, such that the first end of each filament protrudes from the semi-rigid backing.

27. The device of claim 25, wherein the device is designed for use in treating male pattern baldness, and the plurality of filaments protrude from the semi-rigid backing in a pattern which is the same as the pattern of hair growth in a normal human scalp.

28. The device of claim 25, wherein the device is designed for use in implanting genetically modified cells into the skin of a living being, and the filaments protrude from the semi-rigid backing at a sufficient depth to implant the genetically modified cells into target tissue.

29. A method of implanting cells into the skin of a living host, comprising the step of :

a) providing a plurality of filaments, each filament comprising a solid bioabsorbable core and a porous sheath of a bioabsorbable polymer material coating the core,

c) forming the plurality of filaments into a three dimensional matrix,

d) bonding the filaments together.

35. A method of facilitating the growth of new bone comprising the steps of:

a) providing an implantable device comprising a plurality of filaments, each filament comprising a solid bioabsorbable core and a porous sheath of a bioabsorbable material coating the core, wherein the plurality of filaments have been formed into a three dimensional matrix and bonded together,

b) seeding the implantable device with osteoblasts or other osteogenic substances,

f) implanting the device in a site where bone regeneration is desired.

36. A method of continuous delivery of drugs to a living body comprising the steps of:

a) providing a device comprising:

a plurality of filaments, wherein each filament has a first end and a second end, wherein each filament comprises a biocompatible wire core coated by a bioabsorbable porous polymer sheath in which the drug is soluble and permeable, and

a semi-rigid backing comprising a first surface and a reservoir, wherein the second end of each filament is fixed in the semi-rigid backing, such that the first end of each filament protrudes from the first surface and the second end of each filament is in contact with the reservoir;

b) puncturing the skin of the living host with the first end of each filament; and

c) introducing the drug to the living host through the reservoir of the semi-rigid backing and plurality of filaments in contact therewith.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61F 2/04, 2/06, C08J 9/26

A1

(11) International Publication Number: WO 00/45736

(43) International Publication Date: 10 August 2000 (10.08.00)

(21) International Application Number: PCT/US00/03488

(22) International Filing Date: 8 February 2000 (08.02.00)

(30) Priority Data:
60/119,082 8 February 1999 (08.02.99) US

(71) Applicant *(for all designated States except US)*: BIOAMIDE, INC. [US/US]; 15270 67th Street South, Hastings, MN 55033–9173 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: BARROWS, Thomas, H. [US/US]; 1796 Fairview Drive, Austell, GA 30106 (US).

(74) Agents: WELCH, Teresa, J. et al.; Michael Best & Friedrich LLP, Suite 700, One South Pinckney Street, P.O. Box 1806, Madison, WI 53701–1806 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published**
*With international search report.*
*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

(54) Title: FILAMENTARY MEANS FOR INTRODUCING AGENTS INTO CELLS

(57) Abstract

The present invention is directed to filamentary means for the delivery of agents into a living host, and methods for making and using the same. More specifically, the present invention provides new and useful fibers and methods of use of such fibers to implant living cells and other agents into specific tissues, including skin and bone, for the purpose of tissue and organ regeneration, site–specific drug release, transdermal drug delivery, and gene therapy.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/03488

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61F 2/04, 2/06; C08J 9/26
US CL :600/36; 623/1; 521/61; 528/370
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 600/36; 623/1; 521/61; 528/370

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST AND EAST ALL DATA BASE
filament, core, polymer, sheath, drug

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y,P | US 5,997,468 A (WOLFF et al.) 07 December 1999, col. 1, line 66 - col.2, line 33; col. 6, lines 1-6, 49-54; col. 7, lines 25-26, 48-53; col. 9, lines 63-67. | 1-36 |
| Y,P | US 5,993,374 A (KICK) 30 November 1999, abstract; col. 3, line 63 - col. 4, line 12; col. 18, lines 20-30, 53-67; col. 20, lines 36-58; col. 21, lines 52-67; col. 22, Lines 22-35; the claims. | 1-36 |
| Y,P | US 5,898,040 A (SHALABY et al.) 27 April 1999, col. 4, line 66 - col. 5, line 27; col. 8, line 57 - col. 10, line 13. | 1-36 |
| Y | US 5,486,593 A (TANG et al.) 23 January 1996, col. 7, lines 7-37; col. 18, lines 24-33, 46-67; col. 19, lines 1-30. | 1-36 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | | | |
|---|---|---|---|
| * | Special categories of cited documents: | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "A" | document defining the general state of the art which is not considered to be of particular relevance | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "E" | earlier document published on or after the international filing date | "Y" | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "L" | document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" | document member of the same patent family |
| "O" | document referring to an oral disclosure, use, exhibition or other means | | |
| "P" | document published prior to the international filing date but later than the priority date claimed | | |

Date of the actual completion of the international search
10 MAY 2000

Date of mailing of the international search report
13 JUN 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
ISIS GHALI
JOYCE BRIDGERS
PARALEGAL SPECIALIST
CHEMICAL MATRIX
Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)*

09/890844

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



| | | |
|---|---|---|
| Applicant's or agent's file reference<br>16230-9004 | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No.<br>PCT/US00/03488 | International filing date *(day/month/year)*<br>08 FEBRUARY 2000 | Priority date *(day/month/year)*<br>08 FEBRUARY 1999 |
| International Patent Classification (IPC) or national classification and IPC<br>IPC(7): A61F 2/04, 2/06; C08G 63/91; C08J 9/26 and US Cl.: 600/36; 623/1; 521/61; 528/370 | | |
| Applicant<br>BIOAMIDE, INC. | | |

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   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

| | |
|---|---|
| Date of submission of the demand<br>07 SEPTEMBER 2000 | Date of completion of this report<br>12 FEBRUARY 2001 |
| Name and mailing address of the IPEA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>ISIS GHALI<br>Joyce Bridges for<br>Telephone No. (703) 308-1235 |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/03488

## I. Basis of th rep rt

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
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pages _____ , filed with the letter of _____

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☒ the drawings:
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pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the sequence listing part of the description:
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pages _____ , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

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☐ contained in the international application in printed form.

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☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

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**Supplemental B x**
(To be used when th space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII



I. BASIS OF REPORT:

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page(s) NONE, filed with the demand.
and additional amendments:
Pages 3 and 8, filed with the letter of 04 January 2001.

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page(s) NONE, filed with the demand.
and additional amendments:
Pages 21, 24 and 26, filed with the letter of 04 January 2001.

This report has been drawn on the basis of the drawings,
page(s) 1-9, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the sequence listing part of the description:
page(s) NONE, as originally filed.
pages(s) NONE, filed with the demand.
and additional amendments:
NONE

surgery or other painful and expensive implantation techniques, preferably, a technique which produces hair which looks realistic and similar to other hair on the same host. The present invention utilizes a modified form of the bioabsorbable polymeric means developed for use in implantable devices, as described above, to deliver hair follicle cells transdermally and to promote the regeneration of hair therein.

As is shown in the next section, below, the present invention provides a new means for the introduction of agents into a living host, a means which offers several advantages over known means in use today, such as those described briefly above.

## BRIEF SUMMARY OF THE INVENTION

The present invention provides a filamentary means for the introduction of agents into a living host, comprising a filament comprising a solid core and a porous sheath which coats at least a portion of the solid core. When the filamentary means is to be permanently implanted into a living host, both the solid core and the porous sheath are bioabsorbable. When the filamentary means is to be temporarily implanted into the skin of a living host to deliver agents, such as cells, therein, the porous sheath is preferably bioabsorbable but the core need only be biocompatible, not bioabsorabable.

The solid core is preferably wire when the filamentary means is designed to be used to deliver an agent, such as hair follicle cells, into the skin of a living host. The solid core is preferably glass or ceramic when the filamentary means is to be used to deliver an agent, such as cells or pharmaceutical agents, into bone through implantation of the filamentary means into the body of the host.

The porous sheath is preferably in the form of reticulated foam that is well adhered to the core but is capable of separating from the core after a period of several days in vivo. When the agent to be delivered with the filamentary means is a drug, the porous sheath is preferably in the form of a hydrogel and the porosity is on a molecular size scale.

The filamentary means of the present invention provides means for delivery of cells or other agents from outside the body of a living host into the skin of the host, such as a mammal, with minimal trauma to the host. When the filamentary means is comprised of a bioabsorbable core with a bioabsorbable porous sheath which coats at least a portion of the core, the filamentary means can be implanted into specific tissue within a living host and used to deliver agents to the specific tissue when implanted therein. The implantable embodiment of the filamentary means can serve as a surface for osteoblast

skin only long enough for the porous coating to soften and detach from the solid core, but not long enough for the epidermis (8) to grown down the outside of the filament.

FIG. 5b depicts the implant site after the filament core has been removed by pulling out the semi-rigid backing to which it was attached as shown in FIG. 5a. In this case, pulling out the semi-rigid backing and core has resulted in separation of the cell laden porous sheath (2) from the solid core. Sufficient time has elapsed that the epidermis (8) has grown over the implant site, the porous bioabsorbable coating has resorbed, and the implanted cultured cells (6) have survived and are functioning properly.

FIG. 6 is a schematic representation of filaments comprised of a solid core (1) and a porous coating (2) that are bonded together. The process that is utilized to create the bonds between the filaments, for example by heating and cooling, preferably is the same process that is used to create porosity in the coating

FIG. 7 is a scanning electron micrograph (SEM) of the device described in Example 1, at a scale of 1 mm.

FIG. 8 is an SEM of the device described in Example 1, viewing the wires on end showing the exposed tips of the wires and the surrounding coatings of porous, bioabsorbable polymer, at a scale of 100 μm.

FIG. 9 is an SEM of the end of a single wire of the device described in Example 1, showing the morphology of the porous coating, at a scale of 20 μm.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention provides filamentary means for delivery of various agents into a living host, a means comprising a filament comprising a solid core and a bioabsorbable porous sheath. When the solid core is made of bioabsorbable material, it is preferably material selected from the group consisting of glass, ceramic, and polymeric material. When the solid core is made of a biocompatible material, it is preferably material selected from the group consisting of metals or alloys containing the elements of iron, nickel, aluminum, chromium, cobalt, titanium, vanadium, molybdenum, gold, and platinum. The core of the filamentary means is preferably made of bioabsorbable material when the filamentary means is to be used as or as part of an implant to be permanently implanted into the body of a living host. The core of the filamentary means is preferably made of biocompatible material when the filamentary means is to be used in the

CT/US 00/03488
IPEA/US 04 JAN 2001

CLAIMS

1. A filamentary means for the introduction of an agent into a living host, comprising a filament comprising a solid core and a porous sheath, wherein the porous sheath comprises a bioabsorbable sheath polymer which coats at least a portion of the solid core.

2. The filamentary means of claim 1, wherein the solid core comprises a bioabsorbable material selected from the group consisting of a glass, a ceramic, and a polymer.

3. The filamentary means of claim 1, wherein when the solid core is made of a biocompatible material selected from the group consisting of metals or alloys containing the elements of iron, nickel, aluminum, chromium, cobalt, titanium, vanadium, molybdenum, gold, and platinum.

4. The filamentary means of claim 1, wherein the bioabsorbable sheath polymer is selected from the group consisting of poly(lactic acid), poly(glycolic acid), poly(trimethylene carbonate), poly(amino acid)s, tyrosine-derived poly(carbonate)s, poly(carbonate)s, poly(caprolactone), poly(para-dioxanone), poly(ester)s, poly(ester-amide)s, poly(anhydride)s, poly(ortho ester)s, collagen, gelatin, serum albumin, proteins, carbohydrates, poly(ethylene glycol)s, poly(propylene glycol)s, poly(acrylate ester)s, poly(methacrylate ester)s, poly(vinyl alcohol), and copolymers, blends and mixtures of said polymers.

5. The filamentary means of claim 1, further comprising an agent.

6. The filamentary means of claim 5, wherein the agent is living cells.

7. The filamentary means of claim 6, wherein the living cells are obtained from hair follicles.

8. The filamentary means of claim 6, wherein the living cells are genetically engineered cells.

9. The filamentary means of claim 6, wherein the living cells are encapsulated.

10. The filamentary means of claim 5, wherein the agent is cell signaling molecules.

11. The filamentary means of claim 5, wherein the agent is selected from the group consisting of: growth factors, drugs, recombinant molecules, cell recognition factors, cell binding site molecules, cell attachment molecules, cell adhesion molecules, proteins, glycoproteins, carbohydrates, naturally occurring polymers, synthetic polymers, semi-synthetic polymers, and recombinant polymers.

12. The filamentary means of claim 5, wherein the agent is coated on the outer surface of the porous sheath.

13. The filamentary means of claim 5, wherein the agent is mixed, dissolved, or imbedded within the porous sheath.

14. The filamentary means of claim 1, wherein porous sheath defines open pores which are substantially interconnected and large enough to admit the agent.

15. The filamentary means of claim 13, wherein the open pores are large enough to admit molecules ranging in molecular weight from about 500 to about 100,000 Daltons.

16. A method of making a filamentary means for introducing an agent into a living host, comprising the steps of:

a) providing a filamentary solid core,

b) providing a bioabsorbable polymer,

c) providing a pore-forming agent,

d) mixing said bioabsorbable polymer with the pore-forming agent,

e) coating said mixture onto the solid core, and

f) substantially removing or decomposing the pore-forming agent.

17. The method of claim 15, wherein the bioabsorbable polymer is poly(L/DL-lactide).

25. The method of claim 22, wherein the semi-rigid backing of embedded filaments is formed in step (b) according to the additional steps comprising:

inserting the first end of each filament into a mold containing holes that are spaced the same distance apart as hairs on the normal scalp and of a depth sufficient for the first end of each filament to penetrate the skin of a living host when embedded in the semi-rigid backing formed in the remaining steps below,

coating the second end of each filament protruding from the mold with a resin,

curing the resin into a solid polymer,

covering the surface of the polymer with a puncture resistant adhesive tape, and

removing the resulting device, a semi-rigid backing with an array of the first end of filaments protruding therefrom, from the mold.

26. A device for implanting cells into the skin of a living host, comprising:

a) a plurality of filaments, wherein each filament has a first end and a second end, each filament comprising a biocompatible core and a bioabsorbable porous sheath which coats the core at least at the first end of each filament, and

b) a semi-rigid backing with the second end of each of the plurality of filaments embedded therein, such that the first end of each filament protrudes from the semi-rigid backing.

27. The device of claim 25, wherein the device is designed for use in treating male pattern baldness, and the plurality of filaments protrude from the semi-rigid backing in a pattern which is the same as the pattern of hair growth in a normal human scalp.

28. The device of claim 25, wherein the device is designed for use in implanting genetically modified cells into the skin of a living being, and the filaments protrude from the semi-rigid backing at a sufficient depth to implant the genetically modified cells into target tissue.

29. A method of implanting cells into the skin of a living host, comprising the step of :